

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Wedeking et al.

Prior Application: 09/477,072

Prior Filing Date: January 3, 2000

Anticipated Classification of this Application:

Class: 424 Subclass: 9.1, 1.37 & 1.11
Art Unit:

Primary Examiner: D. L. Jones

For: METAL COMPLEXES DERIVATIZED
WITH FOLATE FOR USE IN DIAGNOSTIC
AND THERAPEUTIC APPLICATIONS

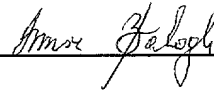
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Dear Sir:

PRELIMINARY AMENDMENT

This is a Preliminary Amendment of co-pending U.S. Application Serial No.
09/477,072 filed January 3, 2000.

Please amend the above-identified application as requested herein.

IN THE SPECIFICATION

Please insert the following on page one of the specification under the title:

-- This application is a divisional of co-pending Application Serial No.
09/477,072 filed January 3, 2000, which in turn is a divisional of
Application Serial No. 09/080,157 filed on May 16, 1998, now U.S.
Patent No. 6,093,382.--

Please amend the specification as follows on the following pages:

on page 13, line 27 cancel "FIG. 5 shows" and replace it with --FIGS. 5 and 5A show --;

on page 13, line 30 cancel "FIG. 6 shows" and replace it with --FIGS. 6 and 6A show--;

on page 13, line 33 cancel "FIG. 7 shows" and replace it with --FIGS. 7, 7A and 7B--;

on page 14, line 8 cancel "FIG. 11 shows" and replace it with --FIGS. 11 and 11A show--;

on page 14, line 14 cancel "FIG. 13 shows" and replace it with --FIGS. 13 and 13A show--;

on page 14, line 16 cancel "FIG. 14 shows" and replace it with --FIGS. 14 and 14A show--;

on page 14, line 25 cancel "FIG. 17 shows" and replace it with --FIGS. 17 and 17A show--;

on page 33, line 7 cancel "Figure 5" and replace it with --Figures 5 and 5A--;

on page 33, line 17 cancel " Figure 6" and replace it with --Figures 6A and 6B--;

on page 33, line 27 cancel " Figure 7" and replace it with -- Figures 7, 7A and 7B--;

on page 35, line 24 cancel " Figure 11" and replace it with --Figures 11 and 11A--;

on page 36, line 19 cancel " Figure 13" and replace it with --Figures 13 and 13A--;

on page 37, line 14 cancel " Figure 14" and replace it with --Figures 14 and 14A--; and

on page 38, line 34 cancel " Figure 17" and replace it with --Figures 17 and 17A--.

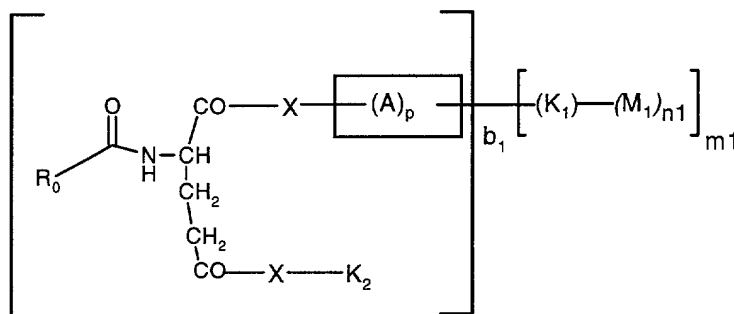
IN THE CLAIMS

Please cancel claims 1-15, 18-20, 22-25, 27, 42-80, and 83-127.

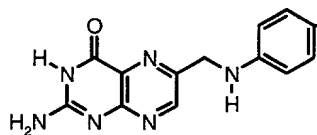
Please amend the following claims as shown.

--16. (Amended) [The composition of claim 11] A diagnostic, therapeutic or radiotherapeutic or chemotherapeutic composition for visualization, therapy, chemotherapy or radiotherapy of tissues or organs that overexpress folate-binding protein comprising:

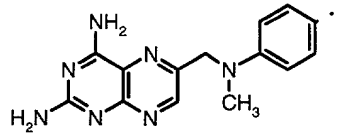
- a) a folate-receptor binding ligand comprising one or more folate-receptor binding moieties, at least one of which is conjugated through its alpha carboxylate via an optional linking group to one or more macrocyclic or non-macrocyclic metal-chelating ligand radicals that are optionally chelated to paramagnetic, superparamagnetic, radioactive or non-radioactive metals for detection outside the body by imaging means for diagnosis or for providing a therapeutic, chemotherapeutic, or radiotherapeutic effect; wherein said folate receptor binding ligand has the structure of formula II:

**II**

wherein R₀ is a folate-receptor binding residue of formula:



or



each X is independently -O-, -S-, -NH-, or -NR₁-;

n₁ is 0 or 1;

b₁ is 1 to 3;

m₁ is 1 to 81;

each K₁ is independently

- a) a macrocyclic or non-macrocyclic metal-chelating ligand radical that is optionally chelated to a paramagnetic, superparamagnetic, radioactive

or non-radioactive metal M₁,

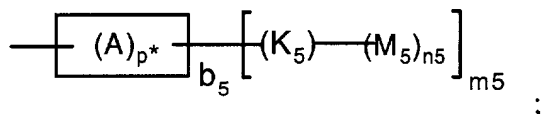
or

b) a chemotherapeutic drug;

-K₂ is -H, -alkyl, -alkenyl, -alkynyl, -alkoxy, -aryl, -alkyl,

-CON(R₂)₂, -glutamate, -polyglutamate, or -K₃,

-K₃ is



wherein

-K₅ is either

a) a macrocyclic or non-macrocyclic metal-chelating ligand that is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal M₅, or

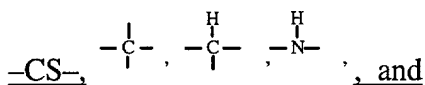
b) a chemotherapeutic drug

n₅ is 0 or 1;

b₅ is 1 to 3;

m₅ is 1 to 81;

-(A)_p- and -(A)_p*- are each independently optional linkers comprising a straight or branched chain wherein the moieties "A" are the same or different and selected from the group consisting of: -CH₂-, -CHR₃-, -CR₄R₅-, -CH=CH-, -CH=CR₆-, >CR₇-CR₈<-, -C=C-, -CR₉=CR₁₀-, -C≡C-, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl (-CO-), -O-, -S-, -NH-, -HC=N-, -CR₁₁=N-, -NR₁₂-,



p and p* are independently 0 to 24,

or -X-[(A)_p]- and -X-[(A)_p]*- may each independently be the group -Q-

wherein -Q- is -[C(R')(R'')]s1-[C(t)(R₂₁)]s2-[C(R₂₂)(R₂₃)]s3-X3-Y-

X4-;

wherein

each s1, s2, s3, and s4 is independently 0 to 2;

each X3, X4, X5, and X6 is independently a single bond, -O-, -S-, or -N(R₂₄)-;

Y is a single bond, -C(R₂₅)(R₂₆)-, or Y1 wherein,

Y1 is -C(=X5)-X6-W-, wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is H, R₂₇, -C(O)OR₂₈, -P(O)(OR₂₉)OH, -P(O)(OR₃₀)OR₃₁, -P(O)(OR₃₂)R₃₃, -P(O)(OH)R₃₄, -C(O)N(R₃₅)(R₃₆), or C(O)NH(R₃₇);

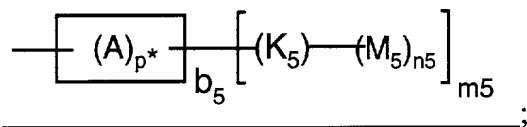
each R' and R'' is independently a single bond, H, alkyl, alkoxy, cycloalkyl,

hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted, each R₃ through R₅, R₇, R₈, R₂₁ through R₂₃, and R₂₅ through R₂₇ is independently H, alkyl, alkoxy, halogen, hydroxy, cycloalkyl, hydroxyalkyl, aryl, or heterocyclo, each of which is optionally substituted;

each R₁, R₂, R₆, R₉ through R₁₂, R₂₄, and R₂₈ through R₃₇ is independently H, alkyl, alkenyl, cycloalkyl, aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle;

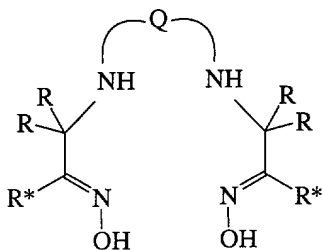
wherein

-K₂ is

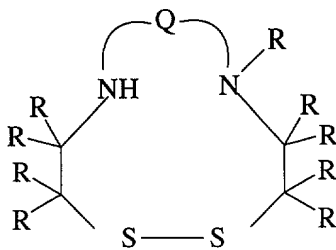


and both -K₁ and -K₅ are macrocyclic or non-macrocyclic metal chelates that are each optionally chelated to radioactive, nonradioactive, paramagnetic or superparamagnetic metals M₁ or M₅;

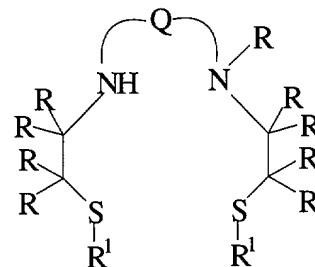
wherein - [(A)p]-K₁ and -[(A)p*]-K₅ are each in their entirety, polydentate ligands radicals of formula **IIIa - IIIc**:



IIIa



IIIb



IIIc

wherein

Q is the group $-(C(RR))_{m1}-Y^1-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_n-$,

wherein

Y¹ and Y² are independently -CH₂-, -NR-, -O-, -S-, -SO-, -SO₂- or -Se-;

n is 0 or 1; and m₁, m₂ and m₃ are integers independently selected from 0 to 4, provided that the sum of m₁ and m₂ is greater than zero;

all R and R* groups are independently -R⁴, -Cl, -F, -Br, -OR⁵, -COOR⁵, -CON(R⁵)₂, -N(R⁵)₂, -alkyl-COOR⁵, -alkyl-C(O)-N(R⁵)₂; -alkyl-N(R⁵)₂; -C(O)OR⁵; -C(O)N(R⁵)₂; -aryl-N(R⁵)₂; acyl; acyloxy; heterocyclo; hydroxyalkyl; -SO₂-R⁵; -alkyl-SO₂-R⁵; or -R³;

wherein

each -[R³]- is, in its entirety, the linking group -[(A)p]- or -[(A)p*]- that serves to couple the metal chelating ligand radical to -X-;

each -R⁴ is independently -H, -alkyl, -alkoxy, -hydroxy, -cycloalkyl, -

hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;
each -R⁵ is independently -H, -alkyl, -aryl, -cycloalkyl or -hydroxyalkyl, each of
which is independently substituted;

with the provisos that a carbon atom bearing an R group is not directly bonded to more
than one heteroatom; and

at least one R or R* group on each -K₁ and -K₅ is -[R³]-;

or a pharmaceutically acceptable salt thereof; in a pharmaceutically acceptable carrier.--

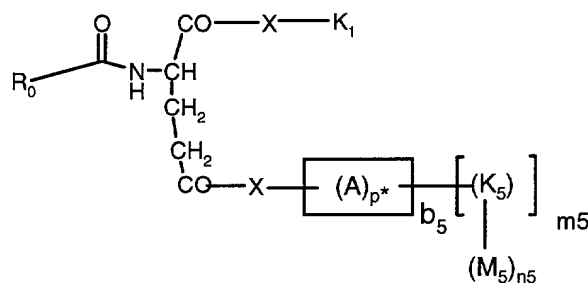
In claim 17, line 1, delete "claim 11" and replace it with --claim 16--.

--21. (Amended) [The compositions of claim 18] A diagnostic, therapeutic or
radiotherapeutic composition for visualization, therapy or radiotherapy of tissues or organs
that overexpress folate-binding protein using nuclear medicine, magnetic resonance
imaging or neutron capture radiotherapy applications comprising:

a) a folate-receptor binding ligand and

b) a pharmaceutically acceptable carrier

wherein said folate-receptor binding ligand has the structure of formula IIb:



IIb

wherein

-K₁ is -H, -alkyl, -alkenyl, -alkynyl, -alkoxy, -aryl, -alkyl, -CON(R₂)₂, -glutamate, or -
polyglutamate;

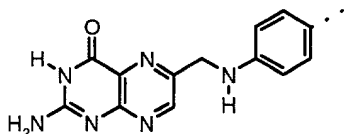
-K₅ is a polydentate metal chelating ligand;

M₅ is a radioactive, paramagnetic or superparamagnetic metal;

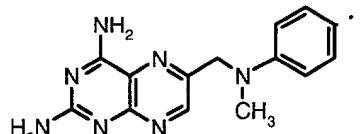
each -X- is independently -O-, -S-, -NH-, or -NR₁-;

b₅ = 1 to 3, m₅ = 1; n₅ is 0 or 1;

-R₀ is a folate-receptor binding residue of formula:



or



each $-(A)p^*-$ is an optional linker independently comprising a straight or branched chain made up of " p^* " individual (A) moieties that are the same or different and are selected from the group consisting of: $-CH_2-$, $-CHR_3-$, $-CR_4R_5-$, $-CH=CH-$, $-CH=CR_6-$, $>CR_7-CR_8<$, $>C=C<$, $-CR_9=CR_{10}-$, $-C\equiv C-$, $-cycloalkylidene-$, $-cycloalkenyl-$, $-arylidene-$, $-heterocyclo-$, carbonyl $(-CO-)$, $-O-$, $-S-$, $-NH-$, $-$

$HC=N-$, $-CR_{11}=N-$, $-NR_{12}-$, $-CS-$, and $\begin{array}{c} | \\ -C- \\ | \end{array}$, $\begin{array}{c} H \\ | \\ -C- \\ | \end{array}$, $\begin{array}{c} H \\ | \\ -N- \\ | \end{array}$;

and p^* is 0 to 24;

or $-X-[A]p^*-$ is, in its entirety, the group $-Q-$

wherein

$-Q-$ is $-[C(R')(R'')]_{s1}-[C(t)(R_{21})]_{s2}-[C(R_{22})(R_{23})]_{s3}-X3-Y-X4-$;

wherein

$s1, s2, s3,$ and $s4$ are independently 0 to 2;

$X3, X4, X5,$ and $X6$ are independently a single bond, $-O-$, $-$

$S-$, or $-N(R_{24})-$;

Y is a single bond, $-C(R_{25})(R_{26})-$, or $-Y1-$

wherein,

$Y1$ is $-C(=X5)-X6-W-$, wherein

W is a single bond, $-alkylidene-$, $-cycloalkylidene-$, $-arylidene-$, $-alkenylidene-$, or $-alkynylidene-$, whose carbon atoms are optionally substituted;

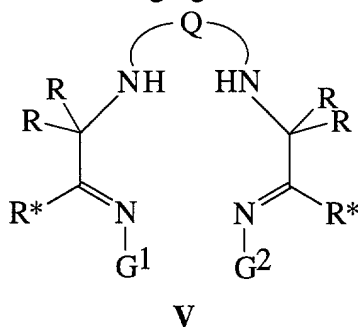
t is $H, R_{27}, -C(O)OR_{28}, -P(O)(OR_{29})OH, -P(O)(OR_{30})OR_{31}, -P(O)(OR_{32})R_{33}, -P(O)(OH)R_{34}, -C(O)N(R_{35})(R_{36}),$ or $C(O)NH(R_{37})$;

each $-R'$ and $-R''$ is independently a single bond, $-H$, $-alkyl$, $-alkoxy$, $-cycloalkyl$, $-hydroxyalkyl$, $-aryl$, or $-heterocyclo$, each of which is optionally substituted,

each $-R_3$ through $-R_5$, $-R_7$, $-R_8$, $-R_{21}$ through $-R_{23}$, and $-R_{25}$ through $-R_{27}$ is independently $-H$, $-alkyl$, $-alkoxy$, $-halogen$, $-hydroxy$, $-cycloalkyl$, $-hydroxyalkyl$, $-aryl$, or $-heterocyclo$, each of which is optionally substituted;

each $-R_1, -R_2, -R_6, -R_9$ through $-R_{12}, -R_{24},$ and $-R_{28}$ through $-R_{37}$ is independently $-H$, $-alkyl$, $-alkenyl$, $-cycloalkyl$, $-aryl$, or a 5- or 6-membered nitrogen or oxygen containing heterocycle;

wherein $-K_5$ is a polydentate metal-chelating ligand radical of formula V:



wherein

Q is the group $-(C(RR))_{m1}-(Y^1)_n-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_{n1}$;

Y^1 and Y^2 are each independently $-CH_2-$, $-NR-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-Se-$;

n and n1 are each independently 0 or 1; and m1, m2 and m3 are independently 0 or an integer from 1 to 4; provided that m1 and m2 are not both 0, that $m1 + m2 + n + n1$ is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each R and R* group is independently: $-H$, $-R^4$; $-alkoxy$; $-hydroxy$; $-halogen$, [especially fluoro,] $-haloalkyl$, $-OR^5$, $-C(O)-R^5$, $-C(O)-N(R^5)_2$, $-N(R^5)_2$, $-N(R^5)-COR^5$, $-alkyl-C(O)-OR^5$, $-alkyl-C(O)-N(R^5)_2$, $-alkyl-N(R^5)_2$, $-alkyl-N(R^5)-COR^5$, $-aryl-C(O)-OR^5$, $-aryl-C(O)-N(R^5)_2$, $-aryl-N(R^5)_2$, $-aryl-N(R^5)-COR^5$, $-nitrile$, $-acyl$, $-acyloxy$, $-heterocyclo$, $-hydroxyalkyl$, $-alkoxyalkyl$, $-hydroxyaryl$, $-arylalkyl$, $-SO_2-R^5$, $-alkyl-SO_2-R^5$, or $-[R^3]-$;

wherein

each $-[R^3]-$ is, in its entirety, the linking group $-[(A)p^*]-$ that serves to couple the metal chelating ligand radical $-K_5$ to $-X-$;

each $-R^4$ is independently $-H$, $-alkyl$, $-alkoxy$, $-hydroxy$, $-cycloalkyl$, $-hydroxyalkyl$, $-aryl$, or $-heterocyclo$, each of which is optionally substituted;

each $-R^5$ is independently $-H$, $-alkyl$, $-aryl$, $-cycloalkyl$ or $-hydroxyalkyl$, each of which is independently substituted;

or

two R groups, or an R group and an R* group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic [(such as fused 1,2-phenyl)] or heterocyclic ring which [may be unsubstituted or] is optionally substituted by one or more groups R or R* groups above;

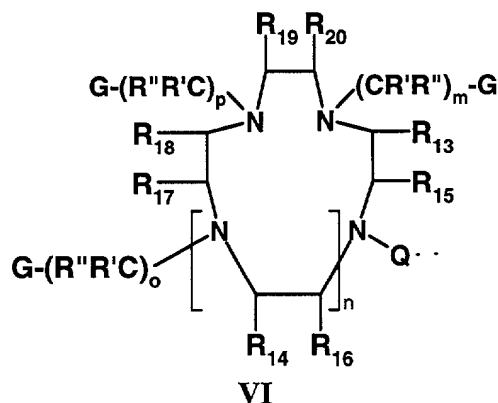
each $-G^1$ and $-G^2$ is independently $-OH$ or $-(NR^6)_2$; with the proviso that at least one of $-G^1$ or $-G^2$ is $-(NR^6)_2$, where each $-R^6$ is independently $-hydrogen$, $-alkyl$, $-aryl$, $-acyl$ or $-[R^3]-$; and

A is a linking group; and p is 0 or a positive integer;

with the proviso that at one to three $-R$, $-R^*$, or $-R^6$ groups is $-[R^3]-$;

or a pharmaceutically acceptable salt thereof.--

--26. (Amended) The composition of claim [18] 21 wherein M_1 or both M_1 and M_5 are paramagnetic or superparamagnetic metals and K_1 or both $-K_1$ and $-K_5$ are enhanced relaxivity polyaza macrocyclic radicals of formula VI:



wherein

n is 0 or 1;

each m, o, and p is independently 1 or 2;

Q is $-\text{C}(\text{R}')(\text{R}'')_{s1}-[\text{C}(\text{t})(\text{R}_{21})]_{s2}-[\text{C}(\text{R}_{22})(\text{R}_{23})]_{s3}-\text{X3}-\text{Y}-\text{X4}-$;

wherein

s1, s2, s3, and s4 are independently 0 to 2;

Y is a single bond, $-\text{C}(\text{R}_{25})(\text{R}_{26})-$, or Y1 wherein,

Y1 is $-\text{C}(=\text{X5})-\text{X6}-\text{W}-$, wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -

alkenylidene-, or -alkynylidene-, whose carbon atoms [may or may not be] are optionally substituted;

t is H, R27, $-\text{C}(\text{O})\text{OR}_{28}$, $-\text{P}(\text{O})(\text{OR}_{29})\text{OH}$, $-\text{P}(\text{O})(\text{OR}_{30})\text{OR}_{31}$,

$-\text{P}(\text{O})(\text{OR}_{32})\text{R}_{33}$, $-\text{P}(\text{O})(\text{OH})\text{R}_{34}$, $-\text{C}(\text{O})\text{N}(\text{R}_{35})(\text{R}_{36})$, or $\text{C}(\text{O})\text{NH}(\text{R}_{37})$;

each G is independently $-\text{C}(\text{O})\text{OR}''$, $-\text{P}(\text{O})(\text{OR}'')\text{OH}$, $-\text{P}(\text{O})(\text{OR}'')_2$,

$-\text{P}(\text{O})(\text{OR}'')\text{R}''$, $-\text{P}(\text{O})(\text{OH})\text{R}''$, $\text{C}(\text{O})\text{N}(\text{R}'')_2$, or $\text{C}(\text{O})\text{NH}(\text{R}'')$;

each -R' and -R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R''' is independently a -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R13 through -R23, and -R25 through -R27 is independently -H, -alkyl, -alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, aryl, or -heterocyclo, each of which is optionally substituted;

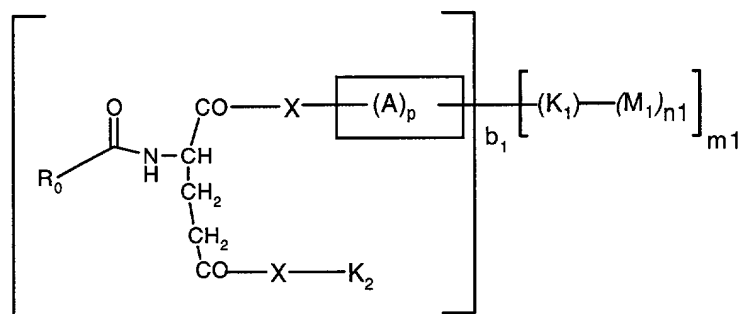
each -R24, and -R28 through -R37 is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

or R13 together with R15, and R17 together with R18, independently form, together with the carbon atoms in the polyazamacrocycle to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which [may be unsubstituted or] are optionally substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which [may be further] are optionally fused to a carbocyclic ring, or R13 and R15 are each hydrogen and R17, together with

R₁₈, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, or R₁₃, together with R₁₅, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R₁₇ and R₁₈ are hydrogen;

or a pharmaceutically acceptable salt thereof.--

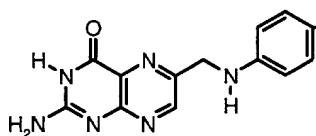
--28. (Amended) A conjugatable polyaza macrocyclic intermediate useful for the preparation of a composition [of claim 27,] for visualization or radiotherapy of tissues or organs that overexpress folate-binding protein using magnetic resonance imaging or neutron capture therapy techniques comprising one or more folate-receptor binding residues conjugated to one or more enhanced relaxivity polyaza macrocyclic radicals which are optionally chelated to a paramagnetic or superparamagnetic metal capable of either being detected outside the body by imaging means for diagnosis or capable of providing a radiotherapeutic effect using neutron capture therapy; wherein said folate-receptor binding compound has the structure of formula IIc:



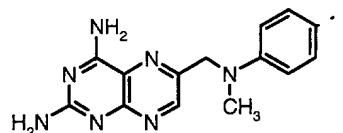
IIc

wherein

R₀ is a folate-receptor binding moiety of formula:



or



each X is independently -O-, -S-, -NH-, or -NR₁-;

n₁ and n₅ are independently 0 or 1;

b₁ and b₅ are independently 1 to 3;

m₁ and m₅ are independently 1 to 81;

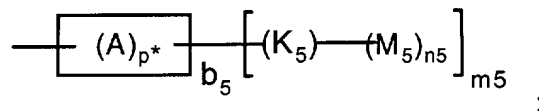
each -K₁ is independently

-H, -alkyl, -alkenyl, -alkynyl, -alkoxy, -aryl, -alkyl, -CON(R₂)₂, -glutamate,

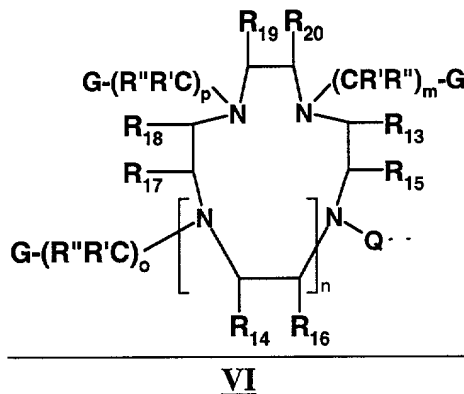
-polyglutamate, or -K₄;

each -K₂ is independently

-H, -alkyl, -alkenyl, -alkynyl, -alkoxy, -aryl, -alkyl, -CON(R₂)₂, -glutamate, -polyglutamate, or -K₃.
-K₃ is



M₁ and M₅ are paramagnetic or superparamagnetic metals; and
-K₄ and -K₅ are each independently enhanced-relaxivity polyaza macrocyclic metal-chelating ligand radicals of formula VI that are optionally chelated to M₁ and M₅:



wherein

n is 0 or 1;

each m, o, and p is independently 1 or 2;

Q is -[C(R')(R'')]s1-[C(t)(R21)]s2--[C(R22)(R23)]s3-X3-Y-X4-; wherein

s1, s2, s3, and s4 are independently 0 to 2;

X3, X4, X5, and X6 are independently a single bond, -O-, -S-, or -N(R24)-;

Y is a single bond, -C(R25)(R26)-, or Y1,

wherein Y1 is -C(=X5)-X6-W-,

wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms are optionally substituted;

t is H, R27, -C(O)OR28, -P(O)(OR29))OH, -P(O)(OR30))OR31,

-P(O)(OR32)R33, -P(O)(OH)R34, -C(O)N(R35)(R36), or

C(O)NH(R37);

each G is independently -C(O)OR'', -P(O)(OR'')OH, -P(O)(OR'')₂,

-P(O)(OR'')R'', -P(O)(OH)R'' C(O)N(R'')₂, or C(O)NH(R'');

each R' and R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each R''' is independently -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -

heterocyclo, each of which is optionally substituted,
each -R₁₃ through -R₂₃, and -R₂₅ through -R₂₇ is independently -H, -alkyl, -
alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -
heterocyclo, each of which is optionally substituted;
each -R₂₄, and -R₂₈ through -R₃₇ is independently -H, -alkyl, -alkenyl, -
cycloalkyl, -aryl, a 5- or 6-membered nitrogen or oxygen containing
heterocycle, each of which is optionally substituted;

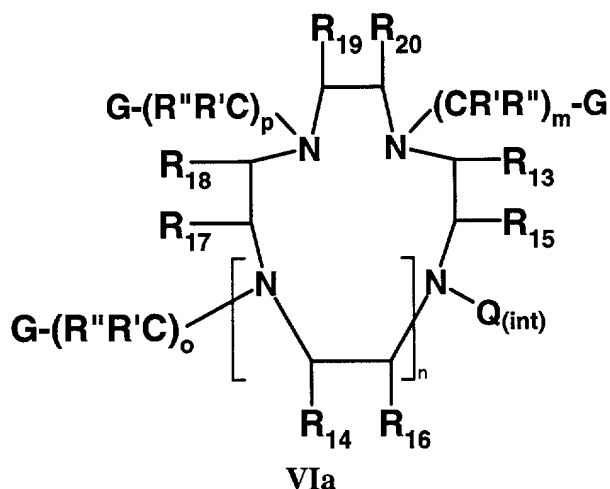
or R₁₃ together with R₁₅, and R₁₇ together with R₁₈, independently form, together
with the carbon atoms in the polyazamacrocyclic to which they are attached, a
fused fully or partially saturated non-aromatic cyclohexyl ring which may be
unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or
hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or
R₁₃ and R₁₅ are each hydrogen and R₁₇, together with R₁₈, forms a fused fully or
partially saturated non-aromatic cyclohexyl ring as defined above, or R₁₃,
together with R₁₅, forms a fused fully or partially saturated non-aromatic
cyclohexyl ring as defined above, and R₁₇ and R₁₈ are hydrogen;

-(A)p- and -(A)p*- are optional linkers each independently comprising a straight or
branched chain made up of moieties that are the same or different and selected from
the group consisting of: -CH₂-, -CHR₃-, -CR₄R₅-, -CH=CH-, -CH=CR₆-,
>CR₇-CR₈<, -C=C-, -CR₉=CR₁₀-, -C≡C-, -cycloalkylidene-, -cycloalkenyl-, -
arylidene-, -heterocyclo-, carbonyl (-CO-), -O-, -S-, -NH-, -HC=N-, -CR₁₁=N-,

-NR₁₂-, -CS-, $\begin{array}{c} | \\ -C- \\ | \end{array}$, $\begin{array}{c} H \\ | \\ -C- \\ | \end{array}$, $\begin{array}{c} H \\ | \\ -N- \\ | \end{array}$; and
p and p* are each individually 0 to 24;

or -X-[(A)p]- or -X-[(A)p*]- in its entirety is the group -Q- as defined above
each -R₃ through -R₅, -R₇ and -R₈ is independently -H, -alkyl, -alkenyl, -alkoxy, -aryl, a
5- or 6-membered nitrogen or oxygen containing heterocycle, halogen, hydroxy or -
hydroxyalkyl; and
each -R₁, -R₂, -R₆, -R₉ through -R₁₂ is independently -H, -alkyl, -alkoxy, -cycloalkyl, -
aryl, -heterocyclo-, -hydroxy or -hydroxyalkyl;
or a pharmaceutically acceptable salt thereof;

said intermediate containing at least one free amine, carboxylate or thiocarboxylate
 functionality that can be used for conjugation to targeting vectors such as folate, said
 intermediates having the structure of formula **VIa**:



wherein

n is 0 or 1;

each m, o, and p is independently 1 or 2;

-Q(int) is a conjugatable amine-, carboxylate- or thiocarboxylate-containing group of formula $-[C(R')(R'')]_{s1}-[C(t)(R_{21})]_{s2}-[C(R_{22})(R_{23})]_{s3}-X_3-Y-X_4$;

wherein

s1, s2, s3, and s4 are independently 0 to 2;

X₃ is a single bond, -O-, -S-, -NH- or -NR₂₄- if Y is present,

or X₃ is -OH, -SH, -NH₂ or -N(R₂₄)H if Y and X₄ are absent;

X₄ is a single bond, -OH, -COOH, -SH, -NHR₂₄ or -NH₂;

Y is a single bond, -C(R₂₅)(R₂₆)-, or Y1

wherein,

Y1 is -C(=X₅)-X₆-W-, wherein

X₅ is =O or =S;

X₆ is a single bond, -SH, -NH(R₃₈), -NH₂

or -OH if W and X₄ are absent, and

is -S-, -O-, -NH-, or -N(R₃₉)-, if W and X₄ are present;

W is a single bond, or is -alkylidene-, -cycloalkylidene-, -arylidene-, -

alkenylidene-, or -alkynylidene-, whose carbon atoms [may or may not

be] are optionally substituted;

t is -H, -R₂₇, -C(O)OR₂₈, -P(O)(OR₂₉)OH, -P(O)(OR₃₀)OR₃₁, -P(O)(OR₃₂)R₃₃, -

P(O)(OH)R₃₄ -C(O)N(R₃₅)(R₃₆), or -C(O)NH(R₃₇);

each -G is independently -C(O)OR'', -P(O)(OR'')OH, -P(O)(OR'')₂, -P(O)(OR'')R'', -

P(O)(OH)R'' -C(O)N(R'')₂, or -C(O)NH(R'');

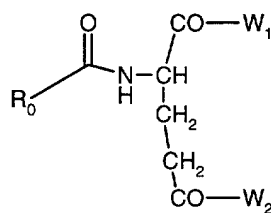
each -R' and -R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R''' is independently -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R₁₃ through -R₂₃, and -R₂₅ through -R₂₇ is independently -H, -alkyl, alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which

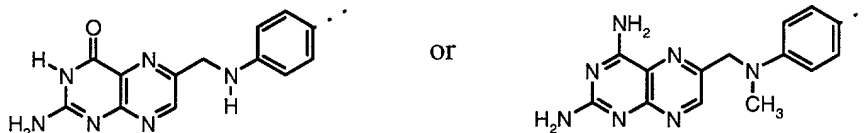
is optionally substituted;
 each -R₂₄, and -R₂₈ through -R₃₉ is independently -H, -alkyl, -alkenyl, cycloalkyl, aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;
 or R₁₃ together with R₁₅, and R₁₇ together with R₁₈, independently form, together with the carbon atoms in the polyazamacrocyclic to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which [may be unsubstituted or] are optionally substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which [may be] are optionally further fused to a carbocyclic ring, or R₁₃ and R₁₅ are each hydrogen and R₁₇, together with R₁₈, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, or R₁₃, together with R₁₅, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, and R₁₇ and R₁₈ are hydrogen;
 or a pharmaceutically acceptable thereof.--

--29. (Amended) A composition comprising folate-receptor binding ligands and a pharmaceutically acceptable carrier for use in nuclear medicine, magnetic resonance imaging, or neutron capture therapy techniques, said folate-receptor binding ligands comprising dendrimeric first-, second-, third-, and fourth- generation conjugates containing one folate-receptor binding [residue] moiety coupled to one or more macrocyclic metal-chelating ligand radicals that are optionally chelated to paramagnetic, superparamagnetic, radioactive or non-radioactive metals [capable of either being detected] for detection outside the body by imaging means for diagnosis or [capable of] for providing a therapeutic or radiotherapeutic effect; wherein said folate-receptor binding compounds have the structure of formulae **VIIa - VIId**:



VIIa - VIId

wherein R₀ is a folate-receptor [residue] moiety of formula:

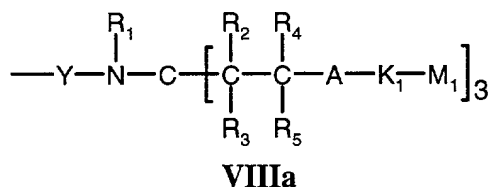


wherein for the first generation dendrimers of formula **VIIa**, bearing one folate-receptor binding [residue] moiety and 3 or 6 metal chelating ligand radicals:

W_1 and W_2 are each independently $-OR'''$, $-SR'''$, $-NR'''R'''$, $-CON(R_2)_2$,
-glutamate, -polyglutamate, or $-K_6$;

wherein each $-R'''$ is independently $[-H, -alkyl, -aryl, -cycloalkyl, -hydroxyalkyl, \text{ or } -heterocyclo]$;

with the proviso that either W_1 , W_2 , or both W_1 and W_2 of formula **VIIa** must
be $-K_6$, where $-K_6$ is a [residue] moiety of formula **VIIIa**:



wherein

Y is [a single bond or] $-Y'-C(=X)-$

wherein

X is $=O$ or $=S$;

Y' is $N(R_6)-Z-$;

wherein

Z is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene-;

A is $-C(=O)-$, $C(=S)$, or $-CH_2-N(R_7)-$;

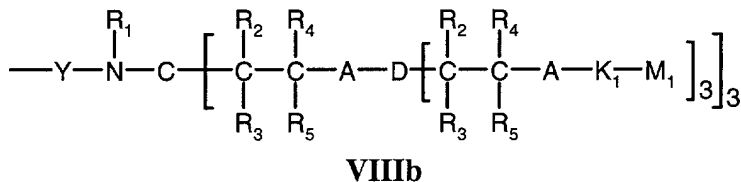
M_1 is a superparamagnetic, paramagnetic, radioactive or non-radioactive
metal, and

K_1 is a macrocyclic metal chelating ligand [residue] moiety;

and,

wherein for second generation dendrimers, bearing one folate receptor binding [residue]
moiety and 9 or 18 macrocyclic metal-chelating ligand radicals and having the structure
of formula **VIIIb**:

W_1 and W_2 are each independently $-OR'''$, $-SR'''$, $-NR'''R'''$, or $-K_7$,
wherein each $-R'''$ is independently $-H, -alkyl, -aryl, -cycloalkyl, -hydroxyalkyl, \text{ or } -heterocyclo$, and $-K_7$ is a residue of formula **VIIIb**;
with the proviso that either W_1 , W_2 , or both W_1 and W_2 must be $-K_7$



wherein

Y is a single bond or $-Y'-C(=X)-$

wherein X is $=O$ or $=S$ and Y' is $-N(R_6)-Z-$;

wherein

Z is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -

arylidene-;

A is -C(O)-, C(S)-, or -CH₂-N(R₇)-;

D is -N(R₆)-C- if A is -C(O)- or -C(S)- or -C(=X₂)-E-N(R₇)-C- if A is -CH₂-N(R₇)-;

wherein

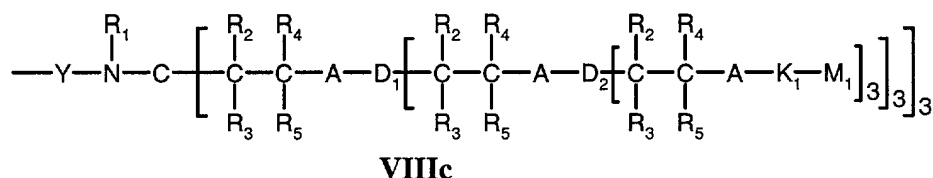
E is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene- and X₂ is =O or =S;

and wherein

for the third generation dendrimeric compounds of formula **VIIIc**; bearing one folate receptor binding residue and 27 or 54 macrocyclic metal-chelating ligand radicals:

W₁ and W₂ are each independently -OR''', -SR''', -NR'''R''', or -K₈ wherein each -R''' is independently -H, -alkyl, -aryl, -cycloalkyl, -hydroxyalkyl, or -heterocyclo, and -K₈ is a [residue] moiety of formula **VIIIc**;

with the proviso that either W₁, W₂, or both W₁ and W₂ of the compounds of formula **VIIIc** must be -K₈ :



wherein,

Y is a single bond or -Y'-C(=X)-

wherein

X is =O or =S;

Y' is -N(R₆)-Z-;

wherein

Z is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene-;

A is -C(O)-, -C(S)-, or -CH₂-N(R₇)-;

D₁ and D₂ are each independently -N(R₆)-C- if A is -C(O)- or -C(S)-, and -C(=X₂)-E-N(R₇)-C- if A is -CH₂-N(R₇)-;

wherein

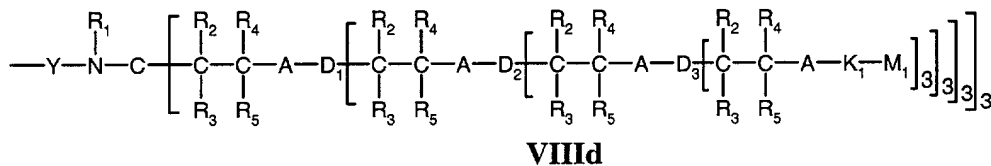
E is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene- and X₂ is =O or =S;

and

wherein for the fourth generation dendrimeric compounds of formula **VIIId**; bearing one folate receptor binding [residue] moiety and 81 or 162 macrocyclic metal-chelating ligand radicals:

W₁ and W₂ are each independently -OR''', -SR''', -NR'''R''' or -K₉,

wherein each R''' is independently -H, -alkyl, -aryl, -cycloalkyl, -hydroxyalkyl, or -heterocyclo and -K₉ is a [residue] moiety of formula **VIIIId**; with the proviso that either W₁, W₂, or both W₁ and W₂ of the compounds of formula **VIIIId** must be -K₉):



wherein Y is a single bond or -Y'-C(=X)-

wherein

X is =O or =S;

Y' is -N(R₆)-Z-;

wherein

Z is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene-;

A is -C(O)-, -C(S)-, or -CH₂-N(R₇)-;

D₁, D₂, and D₃ are each independently -N(R₆)-C if A is -C(O)- or C(S)-, and -C(=X₂)-E-N(R₇)-C if A is -CH₂-N(R₇)-;

wherein E is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene- and X₂ is =O or =S; and

each -R₁ to -R₇ of the compounds of formula **VIIIa-VIIIId** is independently -H, -alkyl, -hydroxyalkyl, -alkoxy, -alkoxyalkyl, -cycloalkyl, or -aryl; each of which is optionally substituted,

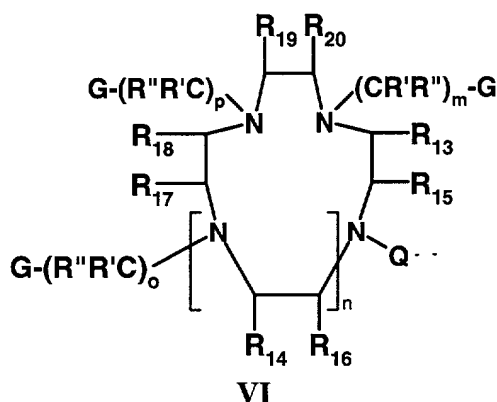
or a pharmaceutically acceptable salt thereof.--

--30. (Amended) The composition of claim 29 wherein W₁ of formula **VIIa - VIId** is a [residue] moiety of formula **VIIIa, VIIIb, VIIIc or VIIIId** and W₂ of formula **VIIa - VIId** is -OR''', -SR''', -NR'''R''' -CON(R₂)₂, -glutamate, or -polyglutamate, wherein each R''' is independently [-H, -alkyl,] -aryl, -cycloalkyl, [-hydroxyalkyl], or -heterocyclo.--

--31. (Amended) The composition of claim 29 wherein W₂ of formula **VIIa - VIId** is a [residue] moiety of formula **VIIIa, VIIIb, VIIIc or VIIIId**; and W₁ of formula **VIIa - VIId** is -OR''', -SR''', -NR'''R''' -CON(R₂)₂, -glutamate, or -polyglutamate, wherein each R''' is independently [-H, -alkyl,] aryl, -cycloalkyl, [hydroxyalkyl,] or -heterocyclo.--

--32. (Amended) The [dendrimeric] composition[s] of claim 29 wherein both W_1 and W_2 of formula VIIa – VIId is a [residue] moiety of formula [VIIIa,] VIIIb, VIIIc or VIId].--

--33. (Amended) The [dendrimeric folate-receptor binding] composition[s] of formula VIIa – VIId of claim 29 [for use in diagnostic imaging using magnetic resonance or nuclear medicine techniques, or for use in radiation- or neutron-capture therapy,] wherein M_1 is a radioactive-, paramagnetic- or superparamagnetic- metal and each K_1 is a macrocyclic metal chelating ligand radical of formula VI:



wherein said metal chelating radical is attached to the remainder of the compound of formulae VIIa - VIId via the free -N(R)- atom of the function -Q- if A is -C(O)- or -C(S)- or through the free -C(O)- atom of the function -Q- if A is -CH₂-N(R₇)-;

wherein -Q- is -[C(R')(R'')]s1-[C(t)(R21)]s2--[C(R22)(R23)]s3-X3-Y-X4;

wherein

s1, s2, s3, and s4 are independently 0 to 2;

X3, X4, X5, and X6 are independently a single bond, -O-, -S-, or -N(R24)-;

Y is a single bond, -C(R25)(R26)-, or Y1,

wherein Y1 is -C(=X5)-X6-W-,

wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms [may or may not be] are optionally substituted;

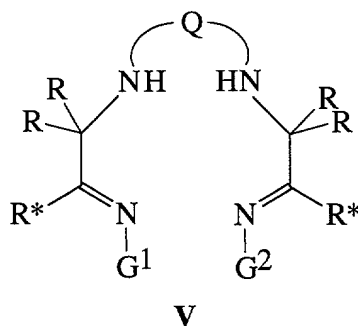
t is H, R27, -C(O)OR28, -P(O)(OR29))OH, -P(O)(OR30))OR31, -P(O)(OR32)R33, -P(O)(OH)R34, -C(O)N(R35)(R36), or C(O)NH(R37);

each G is independently -C(O)OR'', -P(O)(OR'')OH, -P(O)(OR'')₂, -P(O)(OR'')R'', -P(O)(OH)R'' C(O)N(R'')₂, or C(O)NH(R'');

each R' and R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, -

hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,
 each R''' is independently -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo,
 each of which is optionally substituted,
 each -R₁₃ through -R₂₃, and -R₂₅ through -R₂₇ is independently -H, -alkyl, -alkoxy, -
 halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is
 optionally substituted;
 each -R₂₄, and -R₂₈ through -R₃₇ is independently -H, -alkyl, -alkenyl, -cycloalkyl, -
 aryl, or a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of
 which is optionally substituted;
 or a pharmaceutically accepted salt thereof.--

--34. (Amended) The [dendrimeric folate receptor binding] composition of formula
VIIa – VIId of claim 29 wherein M₁ is a radioactive metal and at least one -K₁ is a
 macrocyclic metal chelating ligand radical of formula **V**:



wherein

-Q- is the group $-(C(RR))_{m1}-(Y^1)_n-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_{n1}$;

Y¹ and Y² are each independently -CH₂-, -NR-, -O-, -S-, -SO-, -SO₂- or -Se-;

n and n₁ are each independently 0 or 1; and m₁, m₂ and m₃ are independently 0 or
 an integer from 1 to 4; provided that m₁ and m₂ are not both 0, that m₁ + m₂ +
 n + n₁ is less than 6 and that a carbon atom bearing an R group is not directly
 bonded to more than one heteroatom;

each -R and -R* group is independently: -R⁴; -alkoxy; -hydroxy; -halogen,
 especially fluoro, -haloalkyl, -OR⁵, -C(O)-R⁵, -C(O)-N(R⁵)₂, -N(R⁵)₂, -N(R⁵)-
 COR⁵, -alkyl-C(O)-OR⁵, -alkyl-C(O)-N(R⁵)₂, -alkyl-N(R⁵)₂-, -alkyl-N(R⁵)-
 COR⁵, -aryl-C(O)-OR⁵, -aryl-C(O)-N(R⁵)₂, aryl-N(R⁵)₂-, -aryl-N(R⁵)-COR⁵, -
 nitrile, -acyl, -acyloxy, -heterocyclo, -hydroxyalkyl, -alkoxyalkyl, -hydroxyaryl,
 arylalkyl, -SO₂-R⁵, -alkyl-SO₂-R⁵, or -[R³]-;

wherein

-[R³]- is a linking group -[(A)p]- that links the metal chelating ligand
 radical of formula **V** to the remainder of the molecule of formulae
VIIa through VIId;

wherein -[(A)p]- comprises a straight or branched chain of individual
 moieties that are the same or different and selected from the group
 consisting of: -CH₂-, -CHR₃-, -CR₄R₅-, -CH=CH-, -CH=CR₆-,

$>CR_7-CR_8<$, $-C=C-$, $-CR_9=CR_{10}-$, $-C\equiv C-$, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl ($-CO-$), $-O-$, $-S-$,

$-NH-$, $-HC=N-$, $-CR_{11}=N-$, $-NR_{12}-$, $(-CS-)$, $-\overset{|}{\underset{|}{C}}-$, $-\overset{H}{\underset{|}{\overset{|}{C}}}-$, $-\overset{H}{\underset{|}{N}}-$,
and

p is an integer from 0 to 24;

each $-R^4$ and $-R_3$ through $-R_5$ is independently $-H$, -alkyl, -alkoxy, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each $-R^5$ and R_6 through R_{12} is independently $-H$, -alkyl, -aryl, -cycloalkyl or -hydroxyalkyl, each of which is independently substituted; or

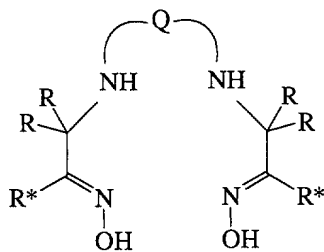
two R groups, or an R group and an R^* group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic [(such as fused 1,2-phenyl)] or heterocyclic ring which [may be unsubstituted] is optionally substituted by one or more [groups] R or R^* groups [above];

each $-G^1$ and $-G^2$ is independently $-OH$ or $-(NR^6)_2$; with the proviso that at least one of $-G^1$ or $-G^2$ is $-(NR^6)_2$, and each $-R^6$ is independently -hydrogen, -alkyl, -aryl, -acyl or $-[R^3]-$;

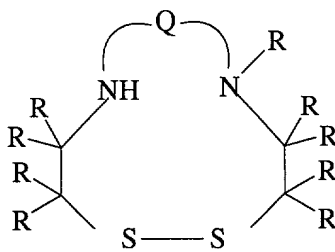
with the proviso that at least one $-R$, $-R^*$, or $-R^6$ group is $-[R^3]-$;

or a pharmaceutically acceptable salt thereof.--

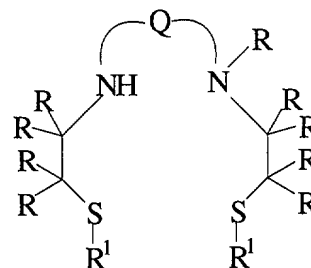
--35. (Amended) The [dendrimeric folate-receptor binding] composition of formula **VIIa - VIId** of claim 29 [for use in nuclear medicine or radiotherapy] wherein M_1 is a radioactive isotope and at least one K_1 is a macrocyclic metal chelating ligand of formula **IIIa - IIIc**:



IIIa



IIIb



IIIc

wherein

Q is the group $-(C(RR))_{m1}-Y^1-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_n-$,

wherein

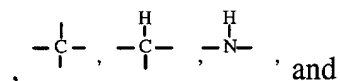
Y^1 and Y^2 are independently $-CH_2-$, $-NR-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-Se-$;

n is 0 or 1; and m_1 , m_2 and m_3 are integers [independently selected] from 0 to 4, provided that the sum of m_1 and m_2 is greater than zero;

all R and R* groups are independently -R⁴, -Cl, -F, -Br, -OR⁵, -COOR⁵, -CON(R⁵)₂, -N(R⁵)₂, -alkyl-COOR⁵, -alkyl-C(O)-N(R⁵)₂, -alkyl-N(R⁵)₂, -C(O)OR⁵, -C(O)N(R⁵)₂, -aryl-N(R⁵)₂, -acyl, -acyloxy, -heterocyclo-, hydroxyalkyl, -SO₂-R⁵, -alkyl-SO₂-R⁵, or -[R³]-;

wherein

- [R³]- is a linking group -[(A)p]- that links the metal chelating ligand of formula **IIIa**, **IIIb**, or **IIIc** to the remainder of the molecule; wherein -[(A)p]- comprises a straight or branched chain of individual moieties that are the same or different and selected from the group consisting of: -CH₂-, -CHR₃-, -CR₄R₅-, -CH=CH-, -CH=CR₆-, >CR₇-CR₈<-, -C=C-, -CR₉=CR₁₀-, -C≡C-, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl -(CO)-, -O-, -S-, -NH-, -HC=N-, -CR₁₁=N-, -NR₁₂-, and -(CS)-



p is an integer from 0 to 24;

each -R⁴ and -R₃ through -R₅ is independently -H, -alkyl, -alkoxy, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

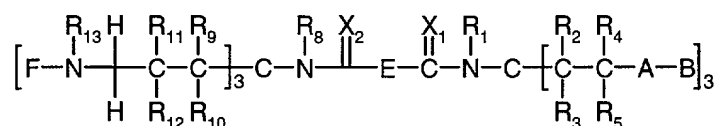
each -R⁵ and -R₆ through R₁₂ is independently -H, -alkyl, -aryl, -cycloalkyl or -hydroxyalkyl, each of which is independently substituted;

with the provisos that a carbon atom bearing an -R group is not directly bonded to more than one heteroatom; and that at least one -R or -R* group on -K₁ is -[R³]-

or a pharmaceutically acceptable salt thereof.--

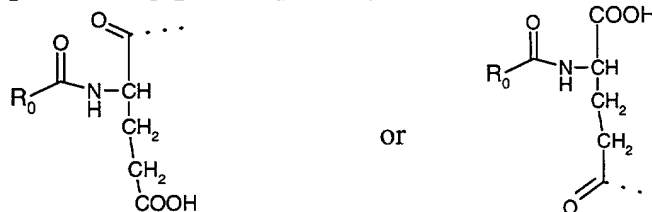
--36. (Amended) A folate-receptor binding ligand comprising dendrimeric first-, second-, third-, and fourth- generation conjugates containing one or more folate-receptor binding [residues] moieties coupled to one or more macrocyclic metal-chelating ligand radicals [that are capable of either being detected] for detection outside the body by imaging means for diagnosis or [capable of] for providing a therapeutic or radiotherapeutic effect, wherein said folate-receptor binding ligands have the structure of formulae **IXa**, **IXb**, **IXc**, and **IXd**, representing dendrimers of generations 1, 2, 3, and 4, respectively,

wherein for the first generation dendrimers of formula **IXa**, bearing three folate and three metal chelating ligand radicals;

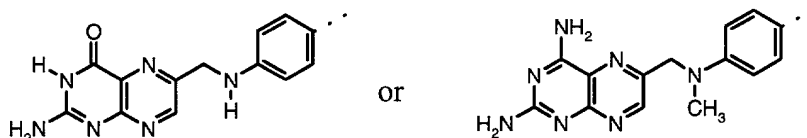


IXa

F is a folate-receptor binding [residue] moiety of formula:



wherein R₀ is a [residue] moiety of formula:



each X₁ through X₄ is independently =O or =S;

each A is -C(O)-, -C(S)-, or -CH₂-N(R₇)-;

E is a single bond, -alkylidene-, -vinylidene-, -cycloalkylidene-, or -arylidene-;

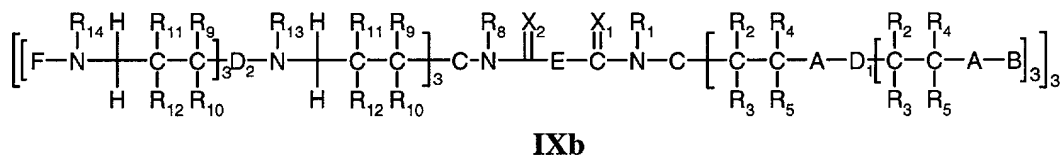
B is a macrocyclic metal-chelating ligand radical that is attached to A via an amide or thioamide bond and is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal;

-R₁, -R₆ through -R₈, -R₁₃, and -R₁₄ are independently -H, -alkyl, -hydroxyalkyl, -cycloalkyl, or -aryl;

-R₂ through -R₅ and -R₉ through -R₁₂ are independently -H, -alkyl, -hydroxyalkyl, -alkoxy, -hydroxyalkyl, -halogen, -cycloalkyl, -aryl or -heterocyclo;

or a pharmaceutically accepted salt thereof;

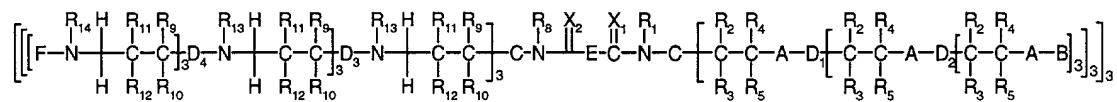
and wherein for the second generation dendrimeric compounds of formula **IXb**, bearing nine folate-receptor binding [residue] moieties and nine metal-chelating ligand radicals:



A, B, E, F, X₁ through X₄ and all -R groups are as defined for the compounds of formula **IXa**;

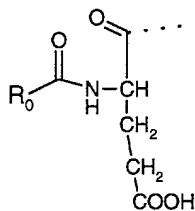
D₁ and D₂ are independently -N(R₆)-C if A is -C(O)- or -C(S)-, and -C(=X₃)-E-N(R₇)-C if A is -CH₂-N(R₇)-;

and wherein for the third generation dendrimeric compounds of formula **IXc**, bearing 27 folate receptor binding [residue] moieties and 27 metal chelating ligand radicals:

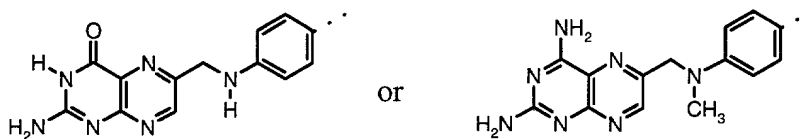
**IXc**

D₁, D₂, D₃, and D₄ are independently -N(R₆)-C if A is -C(O)- or -C(S)-, and -C(=X₃)-E-N(R₇)-C if A is -CH₂-N(R₇)-; and all other groups are defined as above;

--37. (Amended) The [dendrimeric composition] folate-receptor binding ligand of claim 36 wherein F of formulae [IXa,] IXb, IXc, and IXd is a folate-receptor binding [residue] moiety of formula:

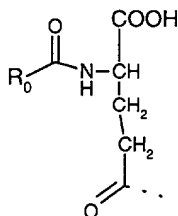


wherein R₀ is a [residue] moiety of formula:

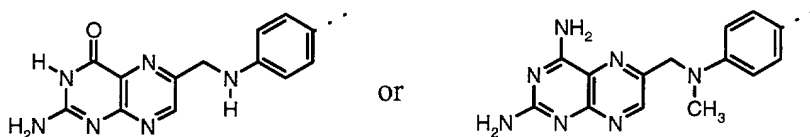


or a pharmaceutically acceptable salt thereof.--

--38. (Amended) The [dendrimeric] folate-receptor binding ligand [composition] of claim 36 wherein F of formulae [IXa,] IXb, IXc, and IXd is a folate receptor binding [residue] moiety of formula:



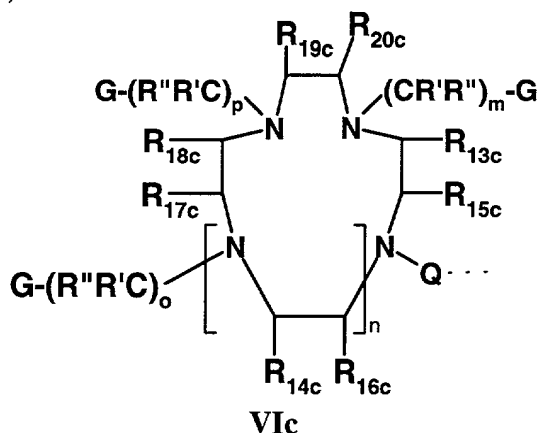
wherein R₀ is a [residue] moiety of formula:



or a pharmaceutically acceptable salt thereof.--

--39. (Amended) The folate-receptor binding ligand [composition] of formulae [IXa,] IXb, IXc, and IXd of claim 36, wherein B is a polyaza macrocyclic ligand radical of

formula **VIc** that is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal,



wherein said macrocyclic ligand radical is attached to A via an amide or thioamide linkage [through a free N atom of the function -Q- if A is -C(O)- or -C(S)- or] through a free -C(O)- group of the function -Q- if A is -CH₂-N(R₇)-;

-Q- is -[C(R')(R'')]s₁-[C(t)(R₂₁)]s₂-[C(R₂₂)(R₂₃)]s₃-X₃-Y-X₄-;

wherein

s₁, s₂, s₃, and s₄ are independently 0 to 2;

-X₃, -X₄, -X₅, and -X₆ are independently a single bond, -O-, -S-, or -N(R₂₄)-;

Y is a single bond, -C(R₂₅)(R₂₆)-, or Y1,

wherein Y1 is -C(=X₅)-X₆-W-,

wherein

W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms [may or may not be] are optionally substituted;

t is H, R₂₇, -C(O)OR₂₈, -P(O)(OR₂₉)OH, -P(O)(OR₃₀)OR₃₁, -P(O)(OR₃₂)R₃₃, -P(O)(OH)R₃₄, -C(O)N(R₃₅)(R₃₆), or C(O)NH(R₃₇);

each G is independently -C(O)OR''', -P(O)(OR''')OH, -P(O)(OR''')₂, -P(O)(OR''')R'', -P(O)(OH)R'' -C(O)N(R''')₂, or -C(O)NH(R''');

each -R' and -R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

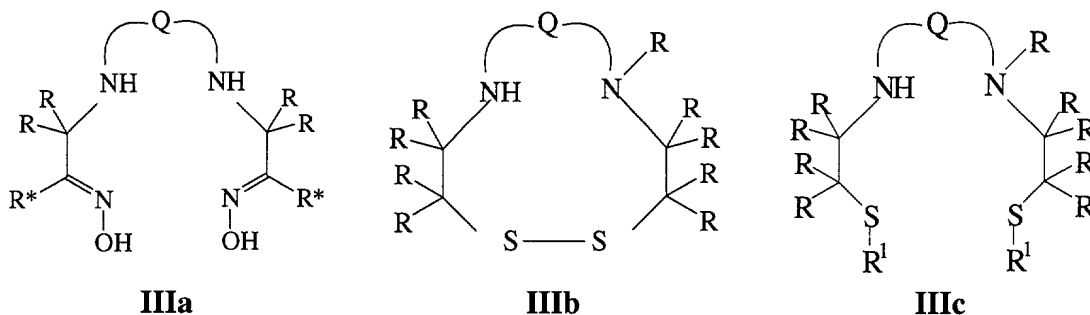
each -R''' is independently -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R_{13c} through -R_{20c}, -R₂₁ through -R₂₃, and -R₂₅ through -R₂₇ is independently -H, -alkyl, -alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each -R₂₄, and -R₂₈ through -R₃₇ is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, a 5- or 6-membered nitrogen or

oxygen-containing heterocycle, each of which is optionally substituted;
or a pharmaceutically accepted salt thereof.--

--40. (Amended) The [dendrimeric] folate-receptor binding ligand [composition] of formulae **IXa**, **IXb**, **IXc**, and **IXd** of claim 36 wherein B is a metal-chelating ligand radical of formula **IIIa** - **IIIc** that is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal:



wherein

Q is the group $-(C(RR))_{m1}-Y^1(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_n-$,

wherein

Y^1 and Y^2 are independently $-\text{CH}_2-$, $-\text{NR}-$, $-\text{O}-$, $-\text{S}-$, $-\text{SO}-$, $-\text{SO}_2-$ or $-\text{Se}-$;

n is 0 or 1; and m1, m2 and m3 are integers [independently selected] from 0 to 4, provided that the sum of m1 and m2 is greater than zero;

all R and R* groups are independently $-\text{R}^4$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{OR}^5$, $-\text{COOR}^5$, $-\text{CON}(\text{R}^5)_2$, $-\text{N}(\text{R}^5)_2$, $-\text{alkyl-COOR}^5$, $-\text{alkyl-C(O)-N}(\text{R}^5)_2$, $-\text{alkyl-N}(\text{R}^5)_2$, $-\text{C(O)OR}^5$, $-\text{C(O)N}(\text{R}^5)_2$, $-\text{aryl-N}(\text{R}^5)_2$, acyl, acyloxy, heterocyclo, hydroxyalkyl, $-\text{SO}_2-\text{R}^5$, $-\text{alkyl-SO}_2-\text{R}^5$, or $-\text{[R}^3\text{]}-$;

wherein $-\text{[R}^3\text{]}-$ is a linking group $-\text{[(A)p]}-$ that couples the metal chelating radical of formula **IIIa**, **IIIb**, or **IIIc** to the remainder of the molecule;

$-\text{[(A)p]}-$ comprises a straight or branched chain of individual moieties that are the same or different and selected from the group consisting of: $-\text{CH}_2-$, $-\text{CHR}_3-$, $-\text{CR}_4\text{R}_5-$, $-\text{CH=CH}-$, $-\text{CH=CR}_6-$, $>\text{CR}_7-\text{CR}_8<$, $-\text{C=C}-$, $-\text{CR}_9=\text{CR}_{10}-$, $-\text{C}\equiv\text{C}-$, $-\text{cycloalkylidene}-$, $-\text{cycloalkenyl}-$, $-\text{arylidene}-$, $-\text{heterocyclo-}$, carbonyl $-\text{(CO)-}$, $-\text{O}-$, $-\text{S}-$, $-\text{NH}-$, $-\text{HC=N}-$, $-\text{CR}_{11}=\text{N}-$,

$-\text{NR}_{12}-$, $-\text{CS}-$, and $-\text{C}-$, $-\text{C}-$, $-\text{N}-$, and

p is an integer from 0 to 24;

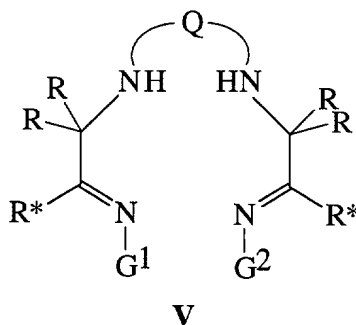
each $-\text{R}^4$ and $-\text{R}_3$ through $-\text{R}_5$ is independently $-\text{H}$, $-\text{alkyl}$, $-\text{alkoxy}$, $-\text{hydroxy}$, $-\text{cycloalkyl}$, $-\text{hydroxyalkyl}$, $-\text{aryl}$, or $-\text{heterocyclo}$, each of

which is optionally substituted;
 each $-R^5$ and $-R_6$ through R_{12} is independently $-H$, $-alkyl$, $-aryl$, $-cycloalkyl$ or $-hydroxyalkyl$, each of which is independently substituted;

[and all other groups are defined as in claim 35,]

with the provisos that a carbon atom bearing an $-R$ group is not directly bonded to more than one heteroatom; and that at least one $-R$ or $-R^*$ group on the metal chelating radical $-K_1$ of formulae **IIIa**, **IIIb**, or **IIIc** is $-[R^3]-$;
 or a pharmaceutically acceptable salt thereof.--

--41. (Amended) The [dendrimeric] folate-receptor binding ligand [composition] of formulae **IXa**, **IXb**, **IXc**, and **IXd** of claim 36, wherein B is a metal-chelating ligand radical of formula **V** that is optionally chelated to a paramagnetic, superparamagnetic, radioactive or non-radioactive metal:



wherein

$-Q-$ is the group $-(C(RR))_{m1}-(Y^1)_n-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_{n1}$;

Y^1 and Y^2 are each independently $-CH_2-$, $-NR-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-Se-$;

n and $n1$ are each independently 0 or 1; and $m1$, $m2$ and $m3$ are [independently] 0 or an integer from 1 to 4; provided that $m1$ and $m2$ are not both 0, that $m1 + m2 + n + n1$ is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each $-R$ and $-R^*$ group is independently: $-R^4$; $-alkoxy$; $-hydroxy$; $-halogen$, [especially fluoro,] $-haloalkyl$, $-OR^5$, $-C(O)-R^5$, $-C(O)-N(R^5)_2$, $-N(R^5)_2$, $-N(R^5)-COR^5$, $-alkyl-C(O)-OR^5$, $-alkyl-C(O)-N(R^5)_2$, $-alkyl-N(R^5)_2$, $-alkyl-N(R^5)-COR^5$, $-aryl-C(O)-OR^5$, $-aryl-C(O)-N(R^5)_2$, $-aryl-N(R^5)_2$, $-aryl-N(R^5)-COR^5$, $-nitrile$, $-acyl$, $-acyloxy$, $-heterocyclo$, $-hydroxyalkyl$, $-alkoxyalkyl$, $-hydroxyaryl$, $-arylalkyl$, $-SO_2-R^5$, $-alkyl-SO_2-R^5$, or $-[R^3]-$;

wherein

$-[R^3]-$ is a linking group $-[(A)p]-$ that links the metal chelating ligand radical of formula **V** to the remainder of the molecule of formulae **IXa**, **IXb**, **IXc**, and **IXd**;

wherein $-[(A)p]-$ comprises a straight or branched chain of individual moieties that are the same or different and are selected from the group

consisting of: $-\text{CH}_2-$, $-\text{CHR}_3-$, $-\text{CR}_4\text{R}_5-$, $-\text{CH}=\text{CH}-$, $-\text{CH}=\text{CR}_6-$, $-\text{CR}_7-\text{CR}_8-$, $-\text{C}=\text{C}-$, $-\text{CR}_9=\text{CR}_{10}-$, $-\text{C}\equiv\text{C}-$, -cycloalkylidene-, -cycloalkenyl-, -arylidene-, -heterocyclo-, carbonyl ($-\text{CO}-$), $-\text{O}-$, $-\text{S}-$, -

$\text{NH}-$, $-\text{HC}=\text{N}-$, $-\text{CR}_{11}=\text{N}-$, $-\text{NR}_{12}-$, $-\text{CS}-$, $-\overset{\text{H}}{\underset{|}{\text{C}}}-$, $-\overset{\text{H}}{\underset{|}{\text{C}}}-$, $-\overset{\text{H}}{\underset{|}{\text{N}}}-$, and p is an integer from 0 to 24;

each $-\text{R}^4$ and $-\text{R}_3$ through $-\text{R}_5$ is independently -H, -alkyl, -alkoxy, -hydroxy, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted;

each $-\text{R}^5$ and R_6 through R_{12} is independently -H, -alkyl, -aryl, -cycloalkyl or -hydroxyalkyl, each of which is independently substituted; or

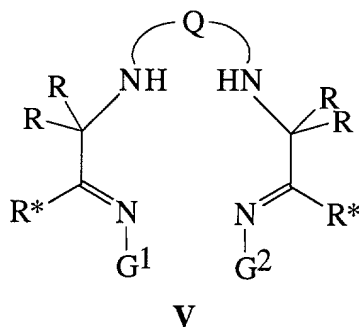
two R groups, or an R group and an R^* group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic [(such as fused 1,2-phenyl)] or heterocyclic ring which may be unsubstituted or substituted by one or more groups of R or R^* [groups above];

each $-\text{G}^1$ and $-\text{G}^2$ is independently -OH or $-(\text{NR}^6)_2$; with the proviso that at least one of $-\text{G}^1$ or $-\text{G}^2$ is $-(\text{NR}^6)_2$, and each $-\text{R}^6$ is independently -hydrogen, -alkyl, -aryl, -acyl or $-\text{[R}^3]-$;

[and all other groups are defined as in claim 80,]

with the provisos that a carbon atom bearing an -R group is not directly bonded to more than one heteroatom and that at least one -R, $-\text{R}^*$, or $-\text{R}^6$ group on the metal chelating radical $-\text{K}_1$ of formula V is $-\text{[R}^3]-$; or a pharmaceutically acceptable salt thereof.--

--81. (Amended) The [A diagnostic or radiotherapeutic] composition of claim 29 wherein W_1 , W_2 or both W_1 and W_2 contain metal chelating ligands of formula V that are chelated to a radioactive metal[.];



wherein

Q is the group $-(C(RR))_{m1}-(Y^1)_n-(C(RR))_{m2}-(Y^2-(C(RR))_{m3})_{n1}$;

Y^1 and Y^2 are each independently $-CH_2-$, $-NR-$, $-O-$, $-S-$, $-SO-$, $-SO_2-$ or $-Se-$;

n and $n1$ are each independently 0 or 1; and $m1$, $m2$ and $m3$ are independently 0 or an integer from 1 to 4; provided that $m1$ and $m2$ are not both 0, that $m1 + m2 + n + n1$ is less than 6 and that a carbon atom bearing an R group is not directly bonded to more than one heteroatom;

each R and R^* group is independently: $-H$, $-R^4$; $-alkoxy$; $-hydroxy$; $-halogen$, especially fluoro, $-haloalkyl$, $-OR^5$, $-C(O)-R^5$, $-C(O)-N(R^5)_2$, $-N(R^5)_2$, $-N(R^5)-COR^5$, $-alkyl-C(O)-OR^5$, $-alkyl-C(O)-N(R^5)_2$, $-alkyl-N(R^5)_2$, $-alkyl-N(R^5)-COR^5$, $-aryl-C(O)-OR^5$, $-aryl-C(O)-N(R^5)_2$, $-aryl-N(R^5)_2$, $-aryl-N(R^5)-COR^5$, $-nitrile$, $-acyl$, $-acyloxy$, $-heterocyclo$, $-hydroxyalkyl$, $-alkoxyalkyl$, $-hydroxyaryl$, $-arylalkyl$, $-SO_2-R^5$, $-alkyl-SO_2-R^5$, or $-[R^3]-$;

wherein

each $-[R^3]-$ is, in its entirety, the linking group $-[(A)p^*]-$ that serves to couple the metal chelating ligand radical $-K_5$ to $-X-$;

each $-R^4$ is independently $-H$, $-alkyl$, $-alkoxy$, $-hydroxy$, $-cycloalkyl$, $-hydroxyalkyl$, $-aryl$, or $-heterocyclo$, each of which is optionally substituted;

each $-R^5$ is independently $-H$, $-alkyl$, $-aryl$, $-cycloalkyl$ or $-hydroxyalkyl$, each of which is independently substituted;

or

two R groups, or an R group and an R^* group, taken together with the one or more atoms to which they are bonded, form a saturated or unsaturated, spiro or fused, carbocyclic (such as fused 1,2-phenyl) or heterocyclic ring which may be unsubstituted or substituted by one or more groups R or R^* groups above;

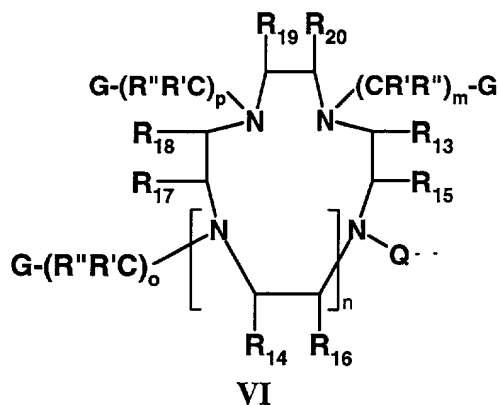
each $-G^1$ and $-G^2$ is independently $-OH$ or $-(NR^6)_2$; with the proviso that at least one of $-G^1$ or $-G^2$ is $-(NR^6)_2$, where each $-R^6$ is independently $-hydrogen$, $-alkyl$, $-aryl$, $-acyl$ or $-[R^3]-$; and

A is a linking group; and p is 0 or a positive integer;

with the proviso that at one to three $-R$, $-R^*$, or $-R^6$ groups is $-[R^3]-$;

or a pharmaceutically acceptable salt thereof.--

--82. (Amended) The [diagnostic] composition of claim 29 wherein W_1 , W_2 or both W_1 and W_2 contain metal chelating ligands of formula V that are chelated to a radioactive metal[.];



wherein

n is 0 [or 1];

each m, o, and p is independently 1 or 2;

Q is $-\text{[C(R')(R'')]s1}-\text{[C(t)(R21)]s2}-\text{[C(R22)(R23)]s3}-\text{X3-Y-X4-}$;

wherein

s1, s2, s3, and s4 are independently 0 to 2;

X3, X4, X5 and X6 are independently a single bond, -O-, -S-, or -N(R24)-;

Y is a [single bond,] -C(R25)(R26)-, or Y1

wherein Y1 is $-\text{C(=X5)-X6-W-}$,

wherein W is a single bond, -alkylidene-, -cycloalkylidene-, -arylidene-, -alkenylidene-, or -alkynylidene-, whose carbon atoms may or may not be substituted;

t is H, R27, -C(O)OR28, -P(O)(OR29))OH, -

P(O)(OR30))OR31, -P(O)(OR32)R33, -P(O)(OH)R34 -C(O)N(R35)(R36), or C(O)NH(R37);

each G is independently -C(O)OR'', -P(O)(OR''')OH, -P(O)(OR''')2, -P(O)(OR''')R'', -P(O)(OH)R''

C(O)N(R''')2, or C(O)NH(R'');

each -R' and -R'' is independently a single bond, -H, -alkyl, -alkoxy, -cycloalkyl, hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R''' is independently a -H, -alkyl, -cycloalkyl, -hydroxyalkyl, -aryl, or -heterocyclo, each of which is optionally substituted,

each -R13 through -R23, and -R24, through -R27 is independently -H, -alkyl, -alkoxy, -halogen, -hydroxy, -cycloalkyl, -hydroxyalkyl, aryl, or -heterocyclo, each of which is optionally substituted;

each -R24, and -R28 through -R37 is independently -H, -alkyl, -alkenyl, -cycloalkyl, -aryl, a 5- or 6-membered nitrogen or oxygen containing heterocycle, each of which is optionally substituted;

or R13 together with R15, and R17 together with R18, independently form, together with the carbon atoms in the poly-aza macrocycle to which they are attached, a fused fully or partially saturated non-aromatic cyclohexyl ring which may be

unsubstituted or substituted by one or more halogen, alkyl, ether, hydroxy, or hydroxyalkyl groups, and which may be further fused to a carbocyclic ring, or R₁₃ and R₁₅ are each hydrogen and R₁₇, together with R₁₈, forms a fused fully or partially saturated non-aromatic cyclohexyl ring as defined above, or R₁₃, together with R₁₅, forms a fused fully or partially saturated non-aromatic cyclohexyl ring [as defined above,] and R₁₇ and R₁₈ are hydrogen; or a pharmaceutically acceptable salt thereof.--

REMARKS

This application is a divisional of co-pending application Serial No. 09/477,072 which is now allowed; and which in turn is a divisional of application Serial No. 09/080,157, now U.S. Patent No. 6,093,382.

During the prosecution of the above-identified applications restriction/election requirements were made and complied with. As a result of the restriction/election, some of the claims were allowed in their entirety and others were amended by canceling the non - elected subject matter from the claims.

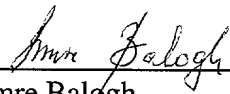
The present, second, divisional application is being submitted with claims containing the previously canceled subject matter.

The specification was also amended to properly describe the Figures which in the immediate divisional application (Div. I) were removed from the specification (wherein they were labeled as Schemes) and placed at the end of the application. Also, as required by the Official Draftsperson in the immediate divisional application (Div. I), some of the Figures were labeled by adding a capital letter (A , B) to the Figures to identify the chemical structures when such structures ran over to the next page.

Favorable consideration of the claims is respectfully requested.

Respectfully submitted,

Date: Dec. 30, 2000



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